

## **PB-PG-0214-3310 – NIHR Research for Patient Benefit Programme – Final report**

**Project title:** The role of apixaban, aspirin and enoxaparin as thromboprophylaxis in patients newly diagnosed with multiple myeloma - an open label randomised feasibility study

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### **Plain language summary**

#### Background and Aim

In recent years, a new anti-clot medicine has become available for use in clinical practice called apixaban. Clinical trials have shown that apixaban is as safe and effective as low molecular weight heparin (LMWH) - an injection based anti-clot medicine, in preventing blood clots for patients undergoing planned bone surgery. Apixaban is available as tablets and provides a solution to overcoming the shortcomings of current preventative therapy available. Very little work has been done to evaluate whether it would be appropriate to use apixaban in myeloma patients who are at risk of developing blood clots. The aim of our study was to assess the feasibility of undertaking a large clinical trial, testing current preventative therapies against apixaban. In addition, we wanted to explore what were patients' understanding and experiences of the current and new preventative agents available.

#### Method

We conducted a small feasibility clinical trial, where patients either received aspirin or LMWH - current gold standard or the new apixaban therapy. In addition, two focus groups were conducted, one comprising of 'general' cancer patients, exploring their understanding of clots in the legs and the lungs and their views on the trial being proposed. The second focus group comprised patients who actually took part in the small trial we conducted and explored their views and experiences of being in the TiMM trial.

#### Results

Ten patients were recruited to the trial and followed up. Patients who were given apixaban did no worse than those patients who received current standard treatments - suggesting it would be reasonable to test apixaban in the myeloma population in a large clinical trial setting. Key messages which emerged from both focus groups were, when initially diagnosed with cancer, the cancer diagnosis is at the forefront of patients minds. Any thoughts on the risk of blood clots are secondary. Those patients who took part in the clinical trial, reported a very positive experience.

#### Conclusions

Our feasibility study results suggest that it could be possible to undertake a large multi-centre clinical trial testing current gold standard treatment with the new medicine - apixaban, however there is insufficient data to confirm whether the design of our study is the most optimal for such a study

## **Keywords**

myeloma, thromboprophylaxis, venous thromboembolism, anticoagulants, low molecular weight heparin, aspirin, apixaban, direct oral anticoagulants

## **Summary of research findings**

### **Background**

Patients with cancer are at high risk of venous thromboembolism (VTE). Active malignancy is associated with an approximate 7 fold increase in VTE, with the incidence in some haematological cancers reported to be as high as 28 fold. Multiple myeloma is a malignant neoplasm of plasma cells that accumulate in the bone marrow leading to bone destruction and marrow failure.

Myeloma is well linked with VTE. A study from the US found an incidence of deep vein thrombosis of 8.7/1000 in patients with myeloma, 3.1/1000 in patients with MGUS, compared to 0.9/1000 in those patients without plasma cell disorders. Recognised risk factors for VTE in this cohort include active disease, cancer chemotherapy, infection, previous VTE, immobility and paraplegia. Thalidomide and lenalidomide have been demonstrated to specifically increase the VTE risk. Neither drug used as mono-therapy significantly increases risk, but when combined with high-dose steroids or cytotoxic agents, the risk of VTE increases significantly. The VTE risk with lenalidomide alone appears to be lower than with thalidomide and the risk of VTE appears to be higher in patients with newly diagnosed myeloma treated with lenalidomide and dexamethasone. In the UK-based Myeloma XI trial, which reflects current treatment practice, the incidence of thrombosis was high (11.8%).

The current British Society of Haematology (BSH) guidelines for myeloma suggest a risk assessment model for the prevention of VTE in myeloma patients treated with thalidomide or lenalidomide. The exact duration of thromboprophylaxis remains unclear but should be guided by risk factors such as active disease (e.g. for the first 4-6 months until disease control achieved) and de-escalated or discontinued unless there are ongoing significant risk factors. The BSH guidelines also stipulate that myeloma patients not receiving thalidomide or lenalidomide may also be considered at risk and thromboprophylaxis may be appropriate and should be considered on a case by case basis.

Thromboprophylactic strategies. In the myeloma population, a number of different VTE thromboprophylactic strategies have been utilised in patients depending on risk; aspirin, LMWH or warfarin (fixed low dose or adjusted dose to achieve an INR of 2–3). The International Myeloma Working Group have also published recommendations pertaining to VTE prophylaxis for myeloma patients. Their recommendations incorporate both patient related and treatment-related risk factors for VTE and mirror the BSH guidelines. The majority of VTE in myeloma patients occur within the first 6 months of treatment, thus thromboprophylaxis is usually prescribed for at least the first 4–6 months of treatment until

disease control is achieved, and may then be de-escalated or discontinued thereafter. In recent years, the availability of the direct oral anticoagulants (DOACs), e.g. apixaban, provide the potential to overcome the shortcomings of current preventative treatment, but to date have not been formally tested for their safety and effectiveness in this setting.

### Aims and Objectives

To evaluate the feasibility of undertaking a multi-centre clinical trial assessing thromboprophylaxis with apixaban 2.5mg bd versus aspirin (in standard risk) or enoxaparin (in high risk) in newly diagnosed myeloma patients.

To explore patients' views on participating in the feasibility clinical trial and their views and understanding of VTE and thromboprophylaxis.

### Methods

2 sub-studies were undertaken. The first was the feasibility clinical trial itself and the second, a qualitative sub-study evaluating patients' views on thromboprophylaxis and their experiences of participating in the clinical trial.

#### Sub-study I - TiMM (Thromboprophylaxis in Multiple Myeloma)

This open-label feasibility clinical trial recruited newly diagnosed myeloma patients and randomised the patients to either aspirin 75mg od or apixaban 2.5mg bd (if standard risk of VTE), or enoxaparin 40mg od or apixaban 2.5mg bd (if high risk of VTE). Patients were followed-up for a maximum of 6 months or until in remission. The primary objective of the trial was safety of apixaban in this specific population. The secondary objectives were the recruitment rate from the eligible population to the trial and the VTE event rate on the different modes of thromboprophylaxis. Trial participants were followed up at the same time as their standard follow-up in the myeloma clinic, for a review of their thromboprophylaxis treatment. Adverse events in relation to the thromboprophylaxis were formally recorded and adjudicated.

#### Sub-study II - focus groups

This sub-study involved the completion of 2 focus groups; (i) one focused on the general perceptions of VTE amongst the general cancer population. This population was recruited from the Guy's Cancer patients panel, and involved exploring patients' views on thromboprophylaxis, their experience of thromboprophylaxis (if any), and what their views were on the proposed feasibility clinical trial. (ii) The second focus group comprised patients who actually took part in the feasibility clinical trial, and explored their views and experiences on taking part and the plans for the next stage of work. Both groups were facilitated by an experienced researcher. The facilitator followed a prespecified topic guide and were recorded. The recordings were transcribed and then thematic analysis was conducted on NVivo version 12.

Regulatory (MHRA) and ethical approvals were sought and approved from both sub-studies.

### Key findings

#### TiMM Clinical Trial

During the recruitment period (12th April 2016-21st April 2017), 32 patients were assessed for eligibility for recruitment to the trial. Twenty-one patients did not meet the eligibility criteria for the study, with 11 not eligible, as they were already prescribed an anticoagulant (8

patients) or antiplatelet (3 patients). Therefore 11 patients met the inclusion criteria and approached to enter the trial with 10 (91%) consenting to take part, suggesting that the design of the study would be acceptable to patients if conducted on a larger scale. The one patient who did not consent gave as a reason an aversion to clinical trials and indeed did not take part in the concurrent Myeloma clinical trial either.

The target for recruitment to TiMM was 40 patients, however, this target was not reached, as the concurrent Myeloma clinical trial in place - the Cardamon Trial, withdrew authorisation of concurrent supportive trial participation (like TiMM) if patients were enrolled in Cardamon. This led to recruitment problems and demonstrates that if a supportive clinical trial were to be done in a larger scale, it needs to be integrated into the primary concurrent Myeloma trial that is running and needs to be designed to account for this.

Of the 10 patients who took part in TiMM, 2 were classed as high risk of VTE, and were randomised to apixaban 2.5mg bd (no patients in TiMM were randomised to enoxaparin). Of these 2 patients, one patient was withdrawn after the baseline visit due to suffering a STEMI. The other patient completed the trial and ceased apixaban after completing their chemotherapy. Eight patients were classified as standard risk and randomised to aspirin or apixaban. Three patients in the apixaban group and 1 patient in the aspirin group completed their thromboprophylaxis. The other patients were withdrawn from the trial for the following reasons; 1 cephalic vein thrombosis in apixaban arm, 1 cephalic vein thrombosis in aspirin arm, 1 rectal bleed, 1 development of atrial fibrillation and 1 disease progression in the aspirin arm. No patients in TiMM suffered a VTE event or a major bleeding event.

#### Focus Groups

The focus group work suggested patients (n=4) newly diagnosed with cancer did not have VTE at the forefront of their minds and were more concerned with their active cancer. Feedback from the patients and carers (n=3) who took part in TiMM suggests that the design of TiMM was acceptable to them and they would take part in a similar study, if invited to do so.

#### Expected impact

The TiMM study suggests that there could be a role for direct oral anticoagulants as a thromboprophylaxis modality in newly diagnosed Myeloma and this should be tested formally in a clinical trial setting, as these agents offer significant practical advantages from a patient and clinician perspective. Key challenges / barriers for undertaking a multi-centre trial, which have been identified through TiMM are:

- (i) As newly diagnosed myeloma patients are treated, their clinical course is varied (due to comorbidities) and can become complicated, e.g. the development of thrombocytopenia, sepsis, renal failure or bleeding, all of which become barriers to continuing prophylaxis therapy
- (ii) There are a number of new therapies emerging in the myeloma field, with uncertain adverse effect profiles, e.g. carfilzomib
- (iii) Line-related thrombosis is not preventable with anticoagulation (already known - seen in 2 patients enrolled to TiMM)

(iv) A lot of uncertainty remains around VTE risk assessment in clinical practice in the myeloma population and the interpretation of international guidelines with respect to this by clinicians.

### **Conclusion**

Our feasibility clinical trial suggests that it is possible to recruit patients in the myeloma setting to a thromboprophylaxis clinical trial, however there is insufficient data to be able to conclude that the trial design we used in TiMM is the optimal design for such a study. Patients who took part in TiMM reported a positive experience and stated that they would take part in a similar study, if invited to do so. Any future multi-centre thromboprophylaxis (supportive) clinical trial in this field should be incorporated into the concurrent national Myeloma trials being conducted at the time, so that co-recruitment is possible.

### **Patient and public involvement**

We had a Myeloma patient on the research team. His contribution to the study was extremely useful, as he provided us with comments on the initial design of our study and then on our patient information leaflets and his views and opinions on the various blood tests we planned to do, and what was and was not acceptable. We also had access to the Guy's cancer panel, which comprised patients with cancer who had an interest in helping with research studies - particularly from a PPI perspective.

### **Data sharing statement**

See link

[\[https://www.nihr.ac.uk/documents/nihr-position-on-the-sharing-of-research-data/12253\]](https://www.nihr.ac.uk/documents/nihr-position-on-the-sharing-of-research-data/12253) for the NIHR position of the sharing of research data. The NIHR strongly supports the sharing of data in the most appropriate way, to help deliver research that maximises benefits to patients and the wider public, the health and care system and which contributes to economic growth in the UK. All requests for data should be directed to the award holder and managed by the award holder.

### **Disclaimer**

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